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April 5, 1999 APR -6 A9:07

Documents Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane.
Rm 1061
Rockville, MD 20852

Re: Docket Number 98D-0994

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the draft Guidance for Industry *BACPAC I Intermediates in Drug Substance Synthesis*. This is a significant step forward in managing manufacturing changes for bulk actives. We appreciate the effort that went into preparing this document and are generally in agreement with the proposal except for the following suggestions and comments:

Line numbers	Comment
15-17	It is not clear why this document does not cover the specifications and methods for the final intermediate while it includes changes in the synthetic steps and manufacturing process for the final intermediate. Once this is published, any changes that are made in the synthesis that affect the specifications will have to revert to the old prior approval supplement process which impedes implementation of minor changes. We recommend inclusion of the specifications and methods for the final intermediate in BACPAC I.
40-48	The comments about FDAMA and forthcoming regulations changes are useful information. However, the status of this work will change and the information is probably better for a cover sheet or appendix rather than in the text of the guidance.
120-121, 243-244, 333-334, 456-457, 512-513	This suggests that if new methods are developed for quantitating existing and new impurities, validation data should be provided to FDA. This is appropriate if these methods are to be used for formally monitoring impurity levels, i.e. if they are going to be new regulatory methods. Often, however, a variety of methods are used to screen for new impurities, and if new impurities are found a variety of actions are initiated, including identification of the impurity and formal validation of methods to quantitate them. The guidance should distinguish between the new regulatory methods and the screening methods. Validation data should not be required for screening methods.

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Line numbers	Comment
124	The selection of ten premodification batches is arbitrary. In some cases, ten would not be available, in others, data on many more batches would be available. We recommend the guidance provide more flexibility. Wording such as "historical data from at least ten premodification batches (if available)" would be provide more flexibility
132-138	There may be new residual organic solvents used in the synthesis of the intermediate. The presence of new residual organic solvents (within the limits provided by ICH Q3C) should be allowed in determining equivalence of the intermediate or the drug substance. This also applies to line p.6, line 149.
156	The principle that the equivalence of impurity profiles can be established by testing any isolated intermediate following the change is a good one and should be maintained.
167	Add methods to the list of changes that can be qualified based on data from pilot scale batches.
170-172	The timing, mechanism, and implications of contacting the reviewing division if equivalence cannot be demonstrated at the commercial site should be clarified.
Footnote 8	This would be better as background in a cover letter, rather than part of the final guidance.
173	This paragraph refers to purification procedures before or after the final intermediate, but does not refer to the final intermediate itself. It may have been the intent to cover this in BACPAC II, but this is not clear as currently written. Given the intent of BACPAC I to cover the final intermediate, we recommend including it here.
190, 295, 381-382, 429-430, 467, 524-525, Attachment A	This suggests that physical properties should be established as equivalent if the drug substance is tested to show equivalence. This is contrary to the idea that testing of the intermediate for impurities is adequate for establishment of equivalence. Testing of the drug substance for impurities and showing that it meets specifications should be all that is required for a change before or including the final intermediate. If the final crystallization and subsequent handling of the drug substance has not changed, physical properties should not be in question.
230	It is presumed that the IQ and OQ information stated here refers to the equipment in the new site, but this should be stated for clarification
262-265	This implies that Annual Report notification is required to use a contract manufacturer previously approved in the application. If the manufacturer was approved, then withdrawn, Annual Report notification is reasonable to go back to that manufacturer. However, no notification should be required if the manufacturer is in the application, and has never been withdrawn.

Line numbers	Comment
266	For the CBE supplements, are the requirements based on individual criteria or a combination of the criteria
313	Some criteria should be established for what constitutes "not significantly different". The SUPAC guidances use the concept of same operating principles. That may be useful here.
332 and 345	Delete ..."or supplement to the application(s), as appropriate", as these do not apply since the filing documentation required is the annual report.
372	Specify for clarity- ...three batches "of the intermediate" made using..
395-397	An explanation or example of what would constitute justification of changes in solvent or reagent changes without test data would be helpful.
417	For clarity, we recommend substituting "intermediate under consideration" for "material".
480	For changes where equivalence is demonstrated, a CBE supplement should be adequate, not prior approval.
503	The requirement for an outline of a change-control protocol is not justified since this is a cGMP/compliance issue and will not provide any added value to the reviewer.
585	For clarity, revise to say "The step in the synthetic process that includes the solution ..." The final solution step is a step in the process, not the solution itself.
589-593	Three times the standard deviation based on a sample size of ten is unlikely to capture all of the normal variation in the historical process. A better range is four times the standard deviation. This is discussed in *Specifications for Chemical and Process Industries*, published by ASQC Chemical and Process Industry Division, Chemical Interest Group (1996)

If you have any questions or if I can be of further assistance, feel free to call on me.

Sincerely,

Harry L. Welles, Ph.D.
Principal Scientist
Regulatory Affairs

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